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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,907	01/22/2004	Kevin Gillman	CT2739NP	6139

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EXAMINER

JOHNSON, JASON H

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/762,907	GILLMAN ET AL.	
	Examiner	Art Unit	
	Jason H. Johnsen	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-4 is/are allowed.
- 6) ☒ Claim(s) 5-7 and 9 is/are rejected.
- 7) ☒ Claim(s) 8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>4/21/04</u> | 6) <input type="checkbox"/> Other: _____ |

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e) to the provisional application 60/444425 filed 02/03/2003.

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60444425 filed 02/03/2003. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A (1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The information disclosure statement (IDS) submitted on 04/19/2004 was filed after the mailing date of the non-provisional application on 01/22/2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statement.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling a method for treating cerebral ischemia/stroke and certain types of brain injuries comprising administering an effective amount of a compound of the formula presented in claim 1, does not reasonably provide enablement for convulsions broadly, epilepsy, asthma, irritable bowel syndrome, migraine headaches, traumatic brain injury broadly, spinal cord injury broadly, sexual dysfunction broadly, carbon monoxide poisoning, and urinary incontinence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation.

The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” In re Wands, 858 F.2d at 737, 8 USPQ 2d at 1404. These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;

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- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is extremely broad due to the large number of disorders responsive to openers of the large conductance calcium-activated potassium channels. Claims 5 is seen to encompass a pharmaceutical composition comprising a compound as defined in claim 1. Claim 6 is drawn to a method of treating all disorders responsive to openers of the large conductance calcium-activated potassium channels. Claim 7, as described in the instant specification, is seen to include ischemia broadly, stroke, convulsions broadly, epilepsy, asthma, irritable bowel syndrome, migraines, traumatic brain injury broadly, spinal cord injury broadly, carbon monoxide poisoning, sexual dysfunction broadly, and urinary incontinence. Claim 9 is seen to broadly encompass all types of traumatic brain injuries. Applicant has not provided sufficient evidence to support a claim drawn to all forms of disorders responsive to openers of large conductance calcium-activated potassium channels.

The nature of the invention

Currently there are no known agents with the ability to effectively treat all diseases arising from dysfunction of cellular membrane polarization and conductance by the modulation of the large conductance (BK) calcium-activated potassium channels. Only recently has the functional roles of calcium-activated potassium channels begun to be elucidated. Faber et al. (The neuroscientist 9:181, 2003). BK channels serve a variety of physiological roles contingent on the Ca^{2+} concentration to which the channels are exposed. Additionally, BK channel activation can also be induced by other factors, such as G-protein, GMP, cGMP, cAMP-

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mediated phosphorylation, and protein kinase A (PKA). In regards to protein kinase A (PKA), both the probability of channel opening and the calcium and voltage sensitivity of the channel are modulated by phosphorylation. However, some types of BK-channels are up regulated by protein kinase A (PKA), whereas other types are down regulated. Xiao-Ming Xia et al (Nature 418:880, 2002). The mechanisms of Ca^{2+} regulation remains largely unknown.

The state of the prior art

In the specification, on page 1, lines 19-25, applicant indicates that several therapeutic approaches for the minimization of stroke-related brain damage have been pursued including inhibitors of AMPA/kainite, N-Methyl-D-aspartate (NMDA) and adenosine reuptake inhibitors. On page 2, lines 1-17, the specification provides a reference that describes the role of potassium channels in regulation of cell membrane potential and modulation of cell excitability. The specification, on page 2, line 12-15, provides a reference that describes the role ions play in controlling the resting membrane potential in most excitable cells and in maintaining the transmembrane voltage near the K^{+} equilibrium potential of about 90mV. On page 3, lines 3-15, the specification provides references on a range of synthetic and naturally occurring compounds with BK opening activity. The prior art does not indicate that the instant compound is useful in treating all disorders responsive to openers of the large conductance calcium-activated potassium channels.

Furthermore, the “state of the prior art” in the pharmaceutical development of natural and synthetic BK-activators is still largely theoretical. The specification, on page 2, lines 20-25, indicates that regulation of large conductance (BK) channels “may be particularly effective” in blocking damaging stimuli, and “may result in protection of neuronal cells under ischemic

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conditions.” Given that large conductance calcium-activated potassium channels play an essential role in the regulation of cell excitability and function, these properties “open a possible role for BK-activators, and/or BK-blockers as effective therapeutic agents for different neurological, urological, respiratory and cardiovascular diseases.” Calderone V (Current Medicinal Chemistry 14:1385-95, 2002).

The level of one of ordinary skill

The level of skill in the art is high, that of a M.D. or PhD.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, in the absence of a showing of treating all disorders responsive to openers of the large conductance calcium-activated potassium channels by the compound of formula I, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula I, due to the unpredictability of the art pertaining to disorders responsive to openers of the large conductance calcium-activated potassium channels.

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The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant provides limited guidance regarding the use of the instant compound in treating all disorders responsive to openers of the large conductance calcium-activated potassium channels. Applicant provides information on biological activity on page 13-20. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of treatment of all disorders responsive to openers of the large conductance calcium-activated potassium channels.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of a method for the treatment of all disorders responsive to openers of the large conductance calcium-activated potassium channels. Applicant provides a biological example on page 15, line 15-18 and limited compound examples on page 22-27 illustrating the procedures for the preparation of intermediates and methods for the preparation of products according to this invention. There is not seen sufficient working examples or data from references on the prior art providing a nexus between that which applicant asserts as proof of a method for treating all disorders responsive to openers of large conductance calcium-activated potassium channels.

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The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art, and the extreme breadth of the claims, one skilled in the art could not use the entire scope of the claimed invention without undue experimentation. It is suggested that applicant limit the disorders responsive to openers of the large conductance calcium-activated potassium channels in claims 5-7 and 9 to disorders that are supported in the specification by biological data.

Claim Objections

Claim 8 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 8 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

Allowable Subject Matter

The prior art does not teach or fairly suggest a substitute indole chemical core derivative with a carbohydrate moiety as set forth in instant claims 1-4.

Conclusion

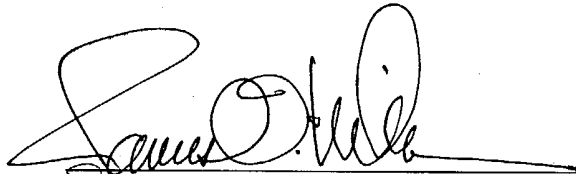
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason H. Johnsen whose telephone number is 571-272-3106. The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason H. Johnsen
October 5, 2004



James O. Wilson
Supervisory Patent Examiner
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